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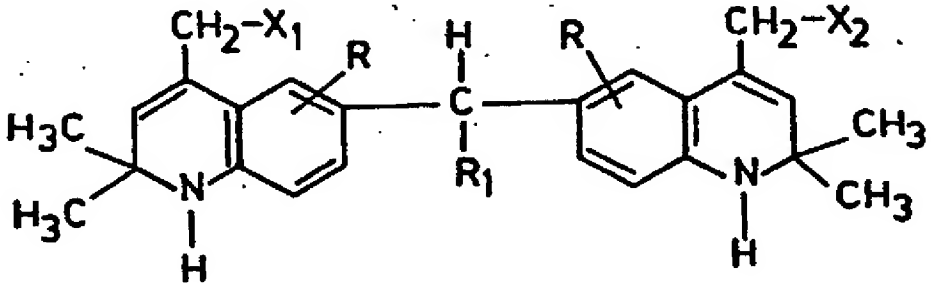
(54) Title: PHARMACEUTICAL COMPOSITIONS AND ALIMENTARY PRODUCTS FOR HUMAN COMSUMPTION FOR THE TREATMENT AND/OR PREVENTION OF DISEASES CAUSED BY FREE RADICAL REACTIONS AND A PROCESS FOR THE INHIBITION OF FREE RADICAL REACTIONS IN THE HUMAN ORGANISM



(I)

(57) Abstract

Pharmaceutical compositions and alimentary products for human consumption for the treatment and/or prevention of diseases caused by free radical reactions, comprising (i) a dihydroquinoline of formula (I), wherein X_1 is a sulfo group or a group of the formula $-SO_2-NH_2$ (a) or $-SO_2-O-Me$ (b) and in the latter M stands for an alkali metal, and X_2 is either hydrogen or its meaning is identical with that of X_1, R_1 stands for a hydrogen atom or an alkyl group, and each R represents independently a halogen or hydrogen atom or a hydroxy, alkoxy, alkyl, aryl, aryloxy or $-NR_2R_3$ group, and in the latter R_2 and R_3 represent, independently from each other, a hydrogen atom or alkyl or aryl group, (ii) ascorbic acid or isoascorbic acid or an alkali metal, calcium or magnesium salt or an ester formed with a fatty acid thereof or a mixture of such compounds, and (iii) optionally a water-soluble inorganic hydrocarbonate salt and/or sodium thiosulfate.

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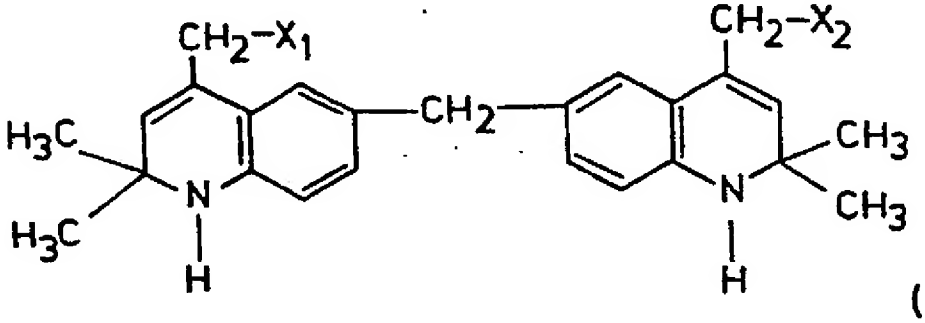
PHARMACEUTICAL COMPOSITIONS AND ALIMENTARY PRODUCTS FOR HUMAN CONSUMPTION FOR THE TREATMENT AND/OR PREVENTION OF DISEASES CAUSED BY FREE RADICAL REACTIONS AND A PROCESS FOR THE INHIBITION OF FREE RADICAL REACTIONS IN THE HUMAN ORGANISM

Technical field

The invention relates to pharmaceutical compositions and alimentary products for human consumption, for the treatment and/or prevention of diseases caused by free radical reactions. The invention relates further to a process for the inhibition of free radical reactions in the human organism.

Background art

It is known for example from the Hungarian patent specification No. 185,208 that the dihydroquinolines of the formula



(II)

wherein X_1 is a sulfo group or a group of the formula

$$— SO_2 — NH_2 \qquad (a) \text{ or}$$

$$— SO_2 — O — Me \qquad (b)$$

and in the latter Me stands for an alkali metal, and

X_2 is either hydrogen or its meaning is identical with that of X_1,

effectively inhibit free radical reactions. They act very effectively in vivo, too and their further advantage resides in their low toxicity.

Our studies on the action of the dihydroquinolines of the formula (II) revealed that they can be used with success in the prevention of diseases caused by free radical reactions, in addition to their favourable therapeutic effect. The following particular advantages of these compounds can be mentioned.

a) They are able to reduce the atherosclerotic index, by preventing risk factors (LDL/HDL and LDL+VLDL/HDL cholesterol fractions), of atherogenesis primarily by substantially increasing the protective HDL fraction and decreasing the detrimental LDL fraction and the VLDL fraction serving as the source of the former, respectively, and the lysosomal enzyme fraction, the presence of which being a precondition of the impairing effect of LDL on the vascular wall.

b) They prevent or significantly reduce the risk of myocardial infarctions in consequence of their ability to inactivate hypoxia-dependent endoperoxide formation, which originates free radicals, as well as their capacity to release oxygen in situ from said endoperoxides.

c) They protect all cellular and subcellular membranes of the human organism, e.g. of the liver, the

brain, and the myocardium, primarily due to their membrane stabilizing effect.

d) They reduce the incidence of malignant neoplasms elicited by carcinogens and nitrosamine precursors, respectively, primarily by inhibiting free radical reactions and by autonitrosification.

e) They reduce the liver impairing action and thrombosis inducing effect of xenobiotics and drugs, e.g. contraceptives.

Of our relevant publications of considerably high number we would like to refer to the following ones:

Zs. Pollák et al: "Effects on serum lipids and biliary cholesterol concentrations of a new dihydroquinoline-type hypolipidemic agent in experimental juvenile atherosclerosis", Proc. 16th ISF Congress, Budapest, 1059 - 1067, 1983;

Sulyok et al: "Liver lipid peroxidation induced by cholesterol and its treatment with a dihydroquinoline type radical scavenger in rabbits", Acta Physiologica Hung., 64, (3-4), 437-442, 1984; and

Fehér et al: "Biochemical markers in carbon tetrachloride and galactosamine induced acute liver injuries; effects of dihydroquinoline type antioxidants", Brit. J. Ex. Path., 63, 394-400, 1982.

The considerable instability of the compounds of the formula (II) (they are readily oxidized particularly on the effect of air and light) inhibits the utilization of their preventive and curative effect. Their oxidative disintegration manifests itself also in blue decolourization. This is probably due to the fact that the methylene bridge linking the two dihydroquinoline moieties is transformed into a hydrol, and one has to reckon also with the transformation of the NH groups containing mobile H-atoms into -N-N-binding.

These transformations also affect the biological

activity of the compounds of the formula (II), i.e. a considerable decrease of the peroxide decomposing ability and scavenger effect of these compounds can be observed. Accordingly, if one wish to utilize the compounds of the formula (II) without the above-mentioned problems, combinations have to be found in which the maintainance of their biological activity is warranted. A sine qua non prerequisite of the preventive combinations warranting regular presence of the active substance in the organism implies the uniform intensity of the biological activity in any of the circumstances of their use. The curative pharmaceutical compositions must, of course, meet similar standards.

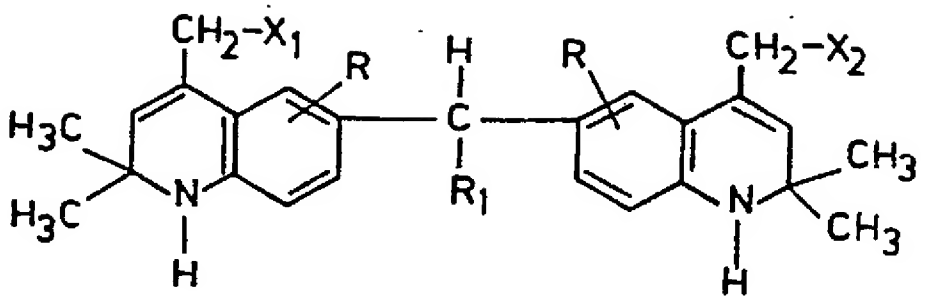
The Hungarian patent specification No. 162,358 discloses the preparation of dihydroquinolines of similar type as well as of pharmaceutical compositions containing such compounds as active agent. The active agents described in this patent specification are dihydroquinoline derivatives in the case of which more than two dihydroquinoline molecules are connected together through methylene bridges, but these molecules are not substituted in the 4th position. The disadvantage of these derivatives resides in their limited solubility or non-solubility in water and, as a consequence, in their limited absorbability.

Disclosure of invention

The invention is aiming at the elaboration of pharmaceutical compositions and alimentary products for human consumption which are free of the above disadvantages, that is, they are absolutely stabile, soluble in water and absorbable.

It has been recognized that the above requirements are met by a composition comprising

(i) a dihydroquinoline of the formula



(I)

wherein

X_1 is a sulfo group or a group of the formula

$$— SO_2 — NH_2 \quad (a) \text{ or}$$

$$— SO_2 — O — Me \quad (b)$$

and in the latter M stands for an alkali metal, and

X_2 is either hydrogen or its meaning is identical with that of X_1,

R_1 stands for a hydrogen atom or a C_{1-4} alkyl group, and

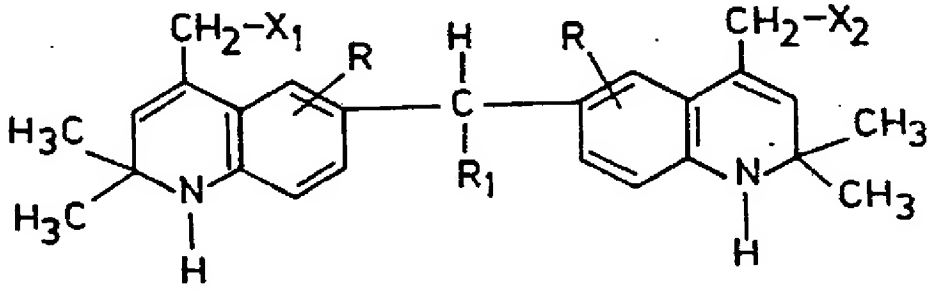
each R represents independently a halogen or hydrogen atom or a hydroxy, C_{1-8} alkoxy, C_{1-12} alkyl, aryl, aryloxy or $-NR_2R_3$ group, and in the latter R_2 and R_3 represent, independently from each other, a hydrogen atom or a C_{1-8} alkyl or aryl group,

(ii) ascorbic acid or isoascorbic acid or an alkali metal, calcium or magnesium salt or an ester formed with a C_{10-20} straight or branched chained fatty acid thereof or a mixture of such compounds, and

(iii) optionally a water-soluble inorganic hydrocarbonate salt and/or sodium thiosulfate. It has been namely recognized that components (i) and (ii) synergically increase the activity of each other and component (iii) protects components (i) and (ii) from the chemical decomposition.

Thus, the present invention relates, on the one hand, to pharmaceutical compositions and alimentary products for human consumption for the treatment and/or prevention of diseases caused by free radical reactions. The compositions of the invention are characterized by comprising

(i) a dihydroquinoline of the formula



(I)

wherein

X_1 is a sulfo group or a group of the formula

$$— SO_2 — NH_2 \qquad (a)$$

$$— SO_2 — O — Me \qquad (b)$$

and in the latter M stands for an alkali metal, and

X_2 is either hydrogen or its meaning is identical with that of X_1,

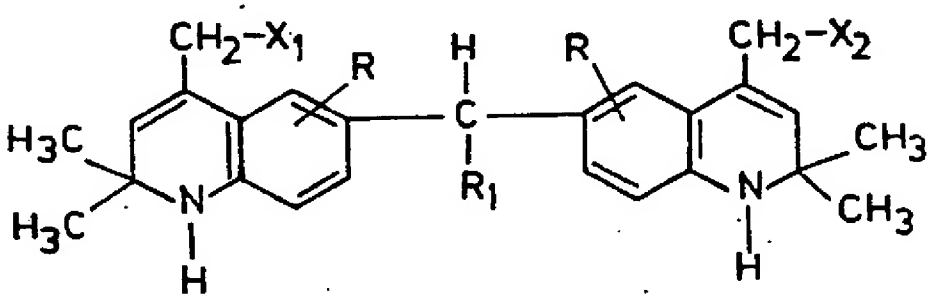
R_1 stands for a hydrogen atom or a C_{1-4} alkyl group, and

each R represents independently a halogen or hydrogen atom or a hydroxy, C_{1-8} alkoxy, C_{1-12} alkyl, aryl, aryloxy or $-NR_2R_3$ group, and in the latter R_2 and R_3 represent, independently from each other, a hydrogen atom or a C_{1-8} alkyl or aryl group,

(ii) ascorbic acid or isoascorbic acid or an alkali metal, calcium or magnesium salt or an ester formed with a C_{10-20} straight or branched chained fatty acid thereof or a mixture of such compounds, taken in an amount of 0.5 to 35 parts by weight based on 100 parts by weight of component (i) , and

(iii) optionally a water-soluble inorganic hydrocarbonate salt, taken in an amount of 1 to 10 parts by weight based on 100 parts by weight of component (i) , and/or sodium thiosulfate, taken in an amount of 0.2 to 5 parts by weight based on 100 parts by weight of component (i).

The present invention relates, on the other hand, to a process for the inhibition of free radical reactions in the human organism. The essence of this process is administering a therapeutically effective amount of a compound of the formula



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wherein

X_1 is a sulfo group or a group of the formula

$$— SO_2 — NH_2 \qquad (a)$$

$$— SO_2 — O — Me \qquad (b)$$

and in the latter M stands for an alkali metal, and

X_2 is either hydrogen or its meaning is identical with that of X_1,

R_1 stands for a hydrogen atom or a C_{1-4} alkyl group, and

each R represents independently a halogen or hydrogen atom or a hydroxy, C_{1-8} alkoxy, C_{1-12} alkyl, aryl, aryloxy or $-NR_2R_3$ group, and in the latter R_2 and R_3 represent, independently from each other, a hydrogen atom or a C_{1-8} alkyl or aryl group,

as component (i) and, simultaneously or separately component (ii) and optionally component (iii) in the above-identified ratios. Said therapeutically effective amount of component (i) is suitably a daily dosage of 0.8 to 1.4 g.

Turning back to formula (I), the alkyl groups and the alkyl moieties of the alkoxy groups can be straight or branched chained. As an example methyl, ethyl, propyl, isopropyl, butyl, octyl and dodecyl groups, respectively, methoxy, ethoxy, propoxy, isopropoxy and octyloxy groups are mentioned. The aryl groups and the aryl moiety of the aryloxy groups are suitably phenyl or naphthyl groups, being optionally substituted by e.g. the above-mentioned alkyl or alkoxy group(s) or

halo atom(s).

The compounds of the formula (I) are either known from the Hungarian patent specification No. 185 208 or are of analogous structure. All the compounds of the formula (I) can be prepared by well-known methods.

The amount of component (i) based on the total amount of the pharmaceutical compositions and alimentary products for human consumption according to the present invention is suitably 0.04 to 75 % by weight. The actual amount of this component depends on the type of the product to be prepared. If e.g. a mineral water is to be prepared, the minimum quantity of component (i) is actually 0.04 % by weight. In the case of preparing a tablet suitable for peroral administration the amount of component (i) can be as high as 75 % by weight. Beyond components (i), (ii) and (iii) the pharmaceutical compositions and the alimentary products for human consumption according to the present invention can contain usual carriers, surfactants and other well-known adjuvants. These pharmaceutical compositions and alimentary products may take the usual forms of such products, said forms being well known to a person skilled in the art.

The pharmaceutical compositions and alimentary products according to the present invention contain preferably sodium or calcium L-ascorbate or palmitic or stearic ascorbate or isoascorbate, more preferably palmitic isoascorbate, as component (ii).

The pharmaceutical compositions and alimentary products according to the present invention contain a component (iii) suitably in the case if a liquid product is prepared. It is highly preferred to use sodium hydrocarbonate and/or sodium thiosulfate as component (iii).

Industrial applicability

The pharmaceutical compositions according to the present invention can be prepared in the form of e.g. tablets, coated tablets, powders or in any other form suitable for peroral administration. Semolina, wheat bran and wheat germ are advantageous vehicles for this purpose, though other conventional vehicles can be used. Tween 80, methylcellulose or polyvinylpyrrolidone can be used as surface-active substances or emulsifiers, respectively. Premixing of the surface-active substance with components (i) and (ii) is preferred. In these compositions the amount of component (i) is adjusted to ensure a daily dosage of suitably 0.8 to 1.4 g., administered in 2 to 6 doses.

In accordance with the present invention one can prepare as alimentary products for human consumption foods and beverages, for example tea, cocoa powder, sweeteners, mineral water or any other beverages or foods for regular consumption containing components (i) and (ii). Prevention of the impairing effect of free radical reactions in the human organism by the regular consumption of these foods and beverages equals that obtained by the administration of the previously mentioned pharmaceutical compositions. Obviously, estimation of the quantity of the daily ingestion of these food and beverage preparations is essential during their production, i.e. the ratio of using component (i) has to be based on the suggested daily dosage of 0.8-1.4 g of this component.

By means of the administration of the pharmaceutical compositions as well as the consumption of alimentary products according the present invention, the permanent presence of components (i) and (ii) in the human organism can be readily achieved. Accordingly, these components (i) and (ii) act as highly potent

scavengers preventing imparing free radical reactions. The effect should be attributed primarily to their action reducing significantly formation of lipid peroxidation end-products and of substances reacting with thiobarbituric acid. In consequence, synthesis of Thromboxane A_2, being harmful from various viewpoints (inducing aggregation, vasoconstriction, damaging of the vascular wall, enhancing plaque formation, and even playing a role in the methastasis formation of malignant tumours), will be inhibited in the organism.

To illustrate these effects of the pharmaceutical compositions and alimentary products according to the present invention, the results of the following in vitro experiments are presented. Lipid oxidation was studied by using the method of Y. T. Lew and A. L. Tappel (Food Technol. 16, 104-106, 1962) in a system containing water, unsaturated fats (oil), haematin, sodium 6,6'--methylene-bis(2,2-dimethyl-1,2-dihydroquinoline-4--methanesulfonate) (abbreviation: MTDQ-DS) and an adequate quantity of sodium L-ascorbate. The so-called induction period being required to reach peroxide number 40 was recorded. Results are shown on following Table.

Change of the induction period in function of the concentrations of the active substances MTDQ-DS and sodium L-ascorbate

MTDQ-DS concentration	Induction period (hour) in the presence of 0 % of sodium L-ascorbate	0.0176 %	0.00176 %
0.02 %	11.3	28	15.4
0.04 %	21	34	24
0 %	0	7.9	1

Data of the Table clearly show that components (i) and (ii) act synergically.

Modes of carrying out the invention

The invention is illustrated by the following examples, without restricting the scope of protection.

Example 1

5.98 g. of sodium 6,6'-methylene-bis(2,2-dimethyl-1,2-dihydroquinoline-4-methanesulfonate) containing 2 moles of crystall water and 1.98 g. of sodium L-ascorbate are mixed with 200 g. of wheat bran. The mixture is homogenized and stored in tightly closed packages. Suggested daily dose amounts to 20 to 40 g.

Example 2

18 g. of sodium 6,6'-methylene-bis(2,2-dimethyl-1,2-dihydroquinoline-4-methanesulfonate) are added to 200 g. of semolina. 0.2 g. of calcium L-ascorbate are rubbed with an identical amount of Tween 80 and added to the above mixture. The mixture is homogenized, granulated with a small amount of starch solution, then dried and pressed into tablets of 1.5 g. The tablets are coated with polyvinylpyrrolidone. Suggested daily dosage: 3x1 tablet.

Example 3

0.9 g. of palmitic isoascorbate are mixed with 0.09 g. of Tween 80 emulsifier and added to 18 g. of sodium 6,6'-methylene-bis(2,2-dimethyl-1,2-dihydroquinoline-4-methanesulfonate salt) and 200 g. of wheat germ. The mixture is homogenized, granulated with starch solution, then dried and pressed into tablets of 0.5 g. Suggested daily dosage: 3x1-2 tablets.

Example 4

200 g. of wheat bran and 0.065 g. of magnesium isoascorbate are mixed and 10 g. of 6,6'-methylene-bis-(2,2-dimethyl-1,2-dihydroquinoline-4-methanesulfonic amide) are added thereto. The mixture is homogenized and the homogeneous powder is distributed into packages of 5 g. Suggested daily dosage: 3 packages.

Example 5

80 g. of sodium 6,6'-methylene-bis(2,2-dimethyl--1,2-dihydroquinoline-4-methanesulfonate) are added to 1000 g. of instant cocoa powder and mixed with 1 g. of sodium L-ascorbate and 0.1 g. of sodiumhydrogencarbonate. The mixture is homogenized. Suggested daily dosage: 3x3.5 g.

Example 6

250 g. of sodium 6,6'-methylene-bis(2,2-dimethyl--1,2-dihydroquinoline-4-methansulfonate) are mixed with 1500 g. of sorbite and 5 g. of calcium L-ascorbate. The mixture is homogenized. The suggested daily dosage of this sweetener amounts to 4 to 6 g.

Example 7

120 g. of sodium 6,6'-methylene-bis(2,2-dimethyl--1,2-dihydroquinoline-4-methansulfonate), 10 g. of sodium isoascorbate and 4 g. sodium thiosulfate are dissolved in 100 l. of mineral water. If the pH-value of the thus--obtained solution is below 7.1, a value of 7.2 to 7.4 is adjusted by using sodium hydrocarbonate. The suggested daily dosage of this mineral water is 0.6 to 0.7 l.

Example 8

One proceeds as in Example 7 but instead of sodium 6,6'-methylene-bis(2,2-dimethyl-1-1,2-dihydroquinoline-4--methansulfonate) sodium 6,6'-methylene-bis(2,2-dimethyl-

-8-hydroxy-1,2-dihydroquinoline-4-methansulfonate) is used.

Example 9

One proceeds as in Example 7 but instead of sodium 6,6'-methylene-bis(2,2-dimethyl-1,2-dihydroquinoline-4--methansulfonate) sodium 6,6'-methylene-bis(2,2-dimethyl--5-amino-1,2-dihydroquinoline-4-methansulfonate) is used.

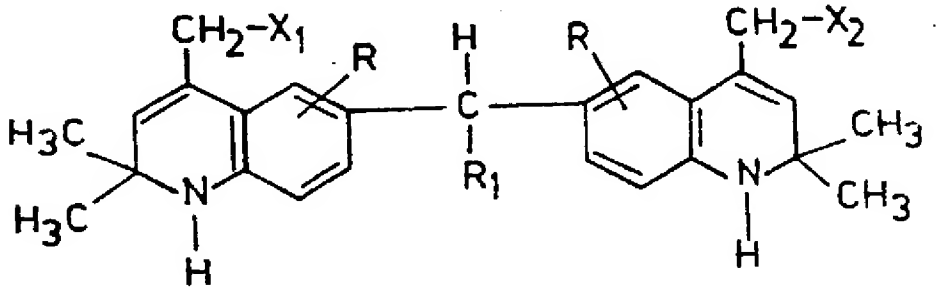
Example 10

One proceeds as in Example 7 but instead of sodium 6,6'-methylene-bis(2,2-dimethyl-1,2-dihydroquinoline-4--methansulfonate) sodium 6,6'-methylene-bis(2,2-dimethyl--7-ethyl-1,2-dihydroquinoline-4-methansulfonate) is used.

What is claimed is:

1. Pharmaceutical compositions and alimentary products for human consumption for the treatment and/or prevention of diseases caused by free radical reactions, c o m p r i s i n g

(i) a dihydroquinoline of the formula



(I)

wherein

X_1 is a sulfo group or a group of the formula

$$— SO_2 — NH_2 \qquad (a)$$ or

$$— SO_2 — O — Me \qquad (b)$$

and in the latter M stands for an alkali metal, and

X_2 is either hydrogen or its meaning is identical with that of X_1,

R_1 stands for a hydrogen atom or a C_{1-4} alkyl group, and

each R represents independently a halogen or

hydrogen atom or a hydroxy, C_{1-8} alkoxy, C_{1-12} alkyl, aryl, aryloxy or $-NR_2R_3$ group, and in the latter R_2 and R_3 represent, independently from each other, a hydrogen atom or a C_{1-8} alkyl or aryl group,

(ii) ascorbic acid or isoascorbic acid or an alkali metal, calcium or magnesium salt or an ester formed with a C_{10-20} straight or branched chained fatty acid thereof or a mixture of such compounds, taken in an amount of 0.5 to 35 parts by weight based on 100 parts by weight of component (i), and

(iii) optionally a water-soluble inorganic hydrocarbonate salt, taken in an amount of 1 to 10 parts by weight based on 100 parts by weight of component (i), and/or sodium thiosulfate, taken in an amount of 0.2 to 5 parts by weight based on 100 parts by weight of component (i).

2. The composition or product as claimed in claim 1, characterized by containing 0.04 to 75 % by weight of component (i).

3. The composition or product as claimed in claim 1, characterized by containing sodium 6,6'-methylene-bis(2,2-dimethyl-1,2-dihydroquinoline-4-methansulfonate) as component (i).

4. The composition or product as claimed in claim 1, characterized by containing sodium L-ascorbate as component (ii).

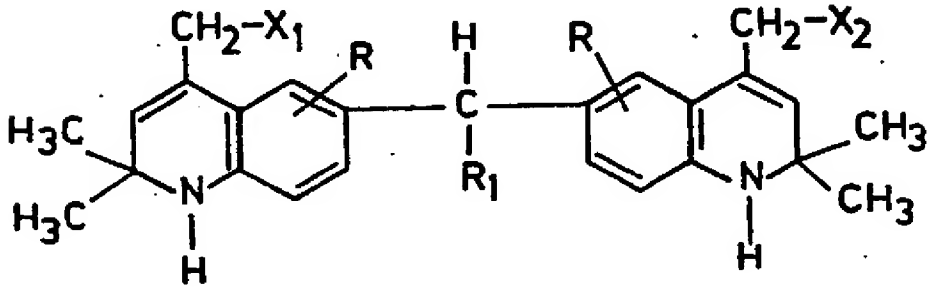
5. The composition or product as claimed in claim 1, characterized by containing calcium L-ascorbate as component (ii).

6. The composition or product as claimed in claim 1, characterized by containing palmitic isoascorbate as component (ii).

7. The composition or product as claimed in

claim 1, c h a r a c t e r i z e d by containing sodium hydrocarbonate as component (iii).

8. Process for the inhibition of free radical reactions in the human organism, c h a r a c t e r i z e d by administering a therapeutically effective amount of a compound of the formula



(I)

wherein

X_1 is a sulfo group or a group of the formula

$$— SO_2 — NH_2 \qquad (a)$$ or

$$— SO_2 — O — Me \qquad (b),$$

and in the latter M stands for an alkali metal, and

X_2 is either hydrogen or its meaning is identical with that of X_1,

R_1 stands for a hydrogen atom or a C_{1-4} alkyl group, and

each R represents independently a halogen or hydrogen atom or a hydroxy, C_{1-8} alkoxy,

C_{1-12} alkyl, aryl, aryloxy or $-NR_2R_3$ group, and in the latter R_2 and R_3 represent, independently from each other, a hydrogen atom or a C_{1-8} alkyl or aryl group,

as component (i) and, simultaneously or separately,

(ii) ascorbic acid or isoascorbic acid or an alkali metal, calcium or magnesium salt or an ester formed with a C_{10-20} straight or branched chained fatty acid thereof or a mixture of such compounds, taken in an amount of 0.5 to 35 parts by weight based on 100 parts by weight of component (i), and

(iii) optionally a water-soluble inorganic hydrocarbonate salt, taken in an amount of 1 to 10 parts by weight based on 100 parts by weight of component (i), and/or sodium thiosulfate, taken in an amount of 0.2 to 5 parts by weight based on 100 parts by weight of component (i).

9. Process as claimed in claim 8, c h a r a c t e r i z e d by administering daily 0.8 to 1.4 g. of component (i).

INTERNATIONAL SEARCH REPORT

International Application No PCT/HU 86/00041

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: A 61 K 31/47,31/375,33/00, A 23 L 3/34, C 07 D 215/04

II. FIELDS SEARCHED

Minimum Documentation Searched [7]	
Classification System	Classification Symbols
Int.Cl.[4]	A 61 K 31/00, A 23 B 4/00,7/00, A 23 D 3/00,5/00, A 23 L 1/00,2/00,3/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
Y	US, A, 4 510 147 (V. BÄR et al.) 09 April 1985 (09.04.85), see claim 1, column 1, line 56 - column 2, line 16, column 2, line 59 - column 3, line 18, column 3, line 66 - column 4, line 65.	(1-6)
Y	H. Janistyn, "Handbuch der Kosmetika und Riechstoffe", third edition, vol. I, published 1978, Dr. Alfred Hüttig Verlag (Heidelberg), see pages 92-93 "Antioxidantien" and "Synergisten", page 111 "Ascorbinsäure" und "Ascorbylester" especially "L(+)-Ascorbinsäure-palmitinsäureester", pages 651-652 "Natriumthiosulfat".	(1-6)
A		(1)
A	DE, B2, 2 243 777 (MATERIAL VEGYI KSZ) 03 May 1978 (03.05.78), see claim; column 4, lines 16-37, column 16, lines 20-26, examples 1-3.	(1,3)

* Special categories of cited documents: [14]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
22 September 1986 (22.09.86)	24 September 1986 (24.09.86)
International Searching Authority	**Signature of Authorized Officer**
AUSTRIAN PATENT OFFICE	

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
Y	Zs. Pollák-Bär et al., "Effects on serum lipids and biliary cholesterol concentrations of a new dihydro-quinoline-type hypolipidemic agent in experimental juvenile atherosclerosis", Proc. 16th ISF Congress, Budapest, published 1983, see pages 1059-1067, especially page 1061, last two lines - page 1062, fist passage, fig. 1; page 1063 "results".	(1-6)
Y	S. Sulyok et al., "Liver lipid peroxidation induced by cholesterol and its treatment with a dihydroquinoline type radical scavenger in rabbits", Acta Physiologica Hung., vol. 64, (3-4), published 1984, see pages 437-442, especially pages 437-439.	(1-6)
Y	J. Fehér et al., "Biochemical markers in carbon tetrachloride and galactosamine induced acute liver injuries; effects of dihydroquinoline type antioxidants", Brit. J. Ex. Path., vol. 63, published 1982, see pages 394-400, especially "Summary", page 394	(1-6)
Y	DE, A1, 2 745 695 (THE WELLCOME FOUNDATION LTD.) 13 April 1978 (13.04.78), see claims 1,11,15.	(1-6)
A	GB, A, 1 125 675 (KYOWA HAKKO KOGYO CO LTD.) 28 August 1968 (28.08.68), see claims 1,6.	(1,4,5)
A	US, A, 4 476 112 (R.W. AUERSANO) 09 October 1984 (09.10.84), see claims 1,3; abstract.	(1,7)
A	FR, A, 2 394 988 (TOPPAN PRINTING CO. LTD.) 19 January 1979 (19.01.79), see claims 1,2, 7,10.	(1,4,7)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☒ Claim numbers 8, 9 because they relate to subject matter not required to be searched by this Authority, namely:

Methods for treatment of the human or animal body by therapy.

2. ☐ Claim numbers ..... because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim numbers ..... because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Anhang zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

Annex to the International Search Report on International Patent Application No. PCT/HU 86/00041

Annexe au rapport de recherche internationale relatif à la demande de brevet international n°.

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned International search report. The Austrian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

La présente annexe indique les membres de la famille de brevets relatifs aux documents de brevets cités dans le rapport de recherche internationale visé ci-dessus. Les renseignements fournis sont donnés à titre indicatif et n'engagent pas la responsabilité de l'Office autrichien des brevets.

Im Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
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